Received: 2 November 2022 | Revised: 1 February 2023 | Accepted: 24 February 2023

DOI: 10.1002/psp4.12956

ARTICLE

A mechanistic modeling platform of SGLT2 inhibition: Implications for type 1 diabetes

Victor Sokolov[1,2,*] | **Tatiana Yakovleva**[1] | **Leonid Stolbov**[1] | **Robert C. Penland**[3] | **David Boulton**[4] | **Joanna Parkinson**[5] | **Weifeng Tang**[4]

[1]M&S Decisions, Moscow, Russia

[2]STU "Sirius", Sochi, Russia

[3]Clinical Pharmacology and Quantitative Pharmacology, Clinical Pharmacology and Safety Sciences, R&D, AstraZeneca, Waltham, Massachusetts, USA

[4]Clinical Pharmacology and Quantitative Pharmacology, Clinical Pharmacology and Safety Sciences, R&D, AstraZeneca, Gaithersburg, Maryland, USA

[5]Clinical Pharmacology and Quantitative Pharmacology, Clinical Pharmacology and Safety Sciences, R&D, AstraZeneca, Gothenburg, Sweden

Correspondence
Victor Sokolov, M&S Decisions, 5 Naryshkinskaya Alley, Building 1, Moscow 125167, Russia.
Email: victor.sokolov@msdecisions.ru

Abstract

Type 1 diabetes mellitus (T1DM) is an autoimmune disease characterized by abnormally high blood glucose concentrations due to dysfunction of the insulin-producing beta-cells in the pancreas. Dapagliflozin, an inhibitor of renal glucose reabsorption, has the potential to improve often suboptimal glycemic control in patients with T1DM through insulin-independent mechanisms and to partially mitigate the adverse effects associated with long-term insulin administration. In this work, we have adapted a systems pharmacology model of type 2 diabetes mellitus to describe the T1DM condition and characterize the effect of dapagliflozin on short- and long-term glycemic markers under various treatment scenarios. The developed platform serves as a quantitative tool for the in silico evaluation of the insulin-glucose-dapagliflozin crosstalk, optimization of the treatment regimens, and it can be further expanded to include additional therapies or other aspects of the disease.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Dapagliflozin is a potent glucose-lowering compound capable of improving glycemic control in both type 2 diabetes mellitus (T2DM) and type 1 diabetes mellitus (T1DM). However, the differences in glycemic control between the diseases add an additional layer of complexity in the application of dapagliflozin in T1DM.

WHAT QUESTION DID THE STUDY ADDRESS?

Which factors define the response of short- and long-term glycemic markers to dapagliflozin administration as an add-on to insulin therapy in T1DM?

WHAT THIS STUDY ADDS TO OUR KNOWLEDGE?

The mechanistic model of T2DM can be adapted to T1DM by replacing endogenous insulin with exogenous insulin and introducing insulin-dependent feedback on glucose production. Decreasing the insulin dose by 15%–38% can counterbalance the average glucose reduction by dapagliflozin treatment.

Victor Sokolov and Tatiana Yakovleva contributed equally to this paper.

HOW MIGHT THIS CHANGE DRUG DISCOVERY, DEVELOPMENT, AND/OR THERAPEUTICS?

The developed platform is a quantitative tool for the in silico trials of combined dapagliflozin/insulin treatment accounting for the heterogeneity in insulin treatment scenarios, meals, and other factors in the actual population, applicable for optimal dose selection, and investigation of the underlying physiological system.

INTRODUCTION

Diabetes mellitus (DM) is a group of diseases characterized primarily by hyperglycemia, predominantly comprising type 1 DM (T1DM) and type 2 DM (T2DM). In healthy adults, the average glucose concentration in arterial blood over 24 h is ~5 mmol/L, fluctuating in a narrow range between 3.1 mmol/L during intense physical activity and 9.2 mmol/L after meals.[1] Such precision is achieved through complex neurohormonal regulation, wherein insulin plays a significant role. Both types of diabetes commonly occur, with T2DM comprising ~95% of all diabetes cases in the United States.[2] T1DM is associated with absolute insulin deficiency caused by a loss of the insulin-producing function of the pancreatic β-cells. In T2DM, insulin deficiency results primarily from a loss of tissue sensitivity to insulin exacerbated by a progressive loss of β-cell function.[3–5] Despite significant advances in treatment options, lifelong insulin therapy remains vital in controlling T1DM. However, long-term insulin treatment is associated with long-term consequences, such as weight gain and its ensuing complications and short-term risks from hypoglycemia, which can be life-threatening; furthermore, less than 30% of adults with T1DM achieve optimal glycemic control, defined as glycated hemoglobin (HbA1c) less than 7%.[6–8]

Dapagliflozin, a potent oral type 2 sodium-glucose cotransporter (SGLT2) inhibitor, initially approved for use in T2DM, was approved in Japan for patients with T1DM to help improve glycemic control through the inhibition of renal glucose reabsorption and stimulation of urinary glucose excretion.[9–12] Dapagliflozin treatment is complementary to insulin administration, as its mechanism of action is different. However, simultaneous treatment with dapagliflozin and insulin adds a layer of complexity to the handling of glycemic control that is maintained through a combination of various types of exogenous insulins. These insulin molecules are analogs of natural insulin, designed with different modes of action, for two different purposes: imitating basal insulin levels and compensating for the high glucose levels after a meal. Thus, they can be classified as long-acting insulins and rapid-acting insulins and distinguished by their pharmacokinetic (PK) properties.

Mathematical models have been used to quantify different aspects of DM and the effects of various interventions for over 50 years, with the glucose-insulin crosstalk being the primary research interest.[13] Recently, an integrated glucose-insulin dapagliflozin (IGID) model, combining the dapagliflozin PK model,[14] renal glucose reabsorption model,[15] well-established integrated glucose-insulin (IGI) model,[16–18] and integrated glucose red blood cell HbA1c (IGRH) model,[19] was developed based on subject-level data from dapagliflozin phase II and phase III clinical trials to characterize both the short-term (within 24 h) and long-term (within weeks) glycemic response to SGLT2 inhibitor treatment in patients with T2DM.[20] As both T2DM and T1DM have a physiological overlap, it is plausible to use this established quantitative platform for T1DM by introducing necessary changes to the model structure. Thus, this research aims to use the existing IGID model to describe glucose homeostasis and dapagliflozin efficacy following the administration of various types of insulin and to identify key factors influencing dapagliflozin's glucose-lowering effects in T1DM.

METHODS

Structural model

The structural model is based on the previously developed IGID model framework[20] and consists of four submodels: (1) IGI; (2) IGRH; (3) renal glucose reabsorption; and (4) dapagliflozin PKs. The IGI submodel, initially designed to describe glucose-insulin homeostasis within a single quantitative framework using bidirectional feedback, was introduced to quantify treatment-mediated short-term responses of plasma glucose and insulin. The IGRH submodel was used for the long-term predictions of dapagliflozin efficacy, expressed in HbA1c %, as a function of average daily blood glucose levels and the life cycle of red blood cells and their progenitors. Dapagliflozin's pharmacodynamic effect, directly associated with the dapagliflozin PK submodel, was introduced in the renal glucose reabsorption submodel as a competitive process where the drug competes with glucose for SGLT2 and type 1

sodium-glucose cotransporter (SGLT1) binding in the S1/S2 and S3 renal tubule compartments, respectively.

Significant discrepancies between T2DM and T1DM are limited to alterations in the IGI part of the system. The most distinctive feature of T1DM is the loss of insulin-secreting function,[21] which provides a strong rationale to exclude insulin production with the associated glycemic control from the model. To compensate for the lack of endogenous insulin secretion and avoid chronic hyperglycemia, patients with T1DM are treated with exogenous insulins. In the model, this is reflected through the introduction of multiple PK models for various types of insulins: rapid-acting insulins, including aspart, lispro, regular insulins 100 and 500, glulisine, and neutral protamine Hagedorn (NPH), as well as long-acting insulin analogs, namely glargine and detemir.

The published one-compartment PK models for aspart,[22] lispro, regular insulins 100 and 500, NPH, and glargine were integrated.[23] Aspart and lispro PK models describe the absorption of both soluble insulin and protamine mixtures through a set of transit compartments or combined first-order and zero-order absorption, respectively. The combined absorption model was also used for insulin glargine. Continuous subcutaneous insulin infusion was emulated using the aspart PK model by replacing the bolus injection with infusion over time. Concentrations of regular and NPH insulins are described using a model with first-order absorption and lag time in case of the latter. The covariates are body weight on volume of distribution and/or clearance, as well as dose affecting bioavailability, absorption, or clearance. The glulisine and detemir PK models were designed de novo, also as one-compartment structures.

Following the implementation of the aforementioned PK models, endogenous insulin concentration in plasma was replaced with the exogenous insulins, with the glucose elimination rate now directly dependent on the concentration of insulin in the central compartment of the respective PK models without delays.

Subsequent changes in the IGI submodel are related to the glucose production rate. The modulation function governing endogenous glucose production during overnight fasting was considered to be specific to T2DM and excluded from the T1DM model.[24] In turn, an additional feedback compartment was introduced to account for the increased gluconeogenesis after exogenous insulin administration in T1DM. This feedback follows the dynamics of the plasma insulin with a delay and allows to describe the short-term plasma glucose recovery after the administration of various mixtures of insulin aspart and lispro. The delay and magnitude of the insulin feedback effect on glucose production were associated with the protamine fraction, with soluble insulins achieving greater potentiation of gluconeogenesis but slower onset of the effect than the high-protamine mixtures. Likewise, insulin-dependent glucose elimination was slower for the protamine-rich solutions.

The final IGID-T1DM model includes 62 ordinary differential equations. A schematic representation of the model is provided in Figure 1. All model equations are provided in the Appendix S1; all parameter values are listed in Table S1.

Data

Insulin PKs and short-term glucose response data

Insulin PK data from adult healthy volunteers or subjects with T1DM were collected for seven types of commonly used insulins through systematic literature search and digitization. The data on aspart (6 sources[25–30]), lispro (7 sources[26,31–36]), glargine (2 sources[37,38]), and regular/NPH insulins (3 sources[32,37,38]) were used to validate the published PK models, integrated into the T1DM platform. Glulisine (1 source[39]) and detemir (2 sources[40,41]) data were used in the development of the respective PK models, because no simple empirical PK model was publicly available for these two products. For lispro and aspart insulin, data were available for both soluble formulations and different protamine mixtures; continuous subcutaneous insulin infusion data were available for aspart. Short-term glucose response data were collected under aspart and lispro insulin treatment with different protamine fractions (3 sources[27,28,35]) and were subsequently used to identify the parameters of insulin feedback on glucose production.

Long-term glucose and HbA1c response data

Individual glucose and HbA1c data from two phase III studies in patients with T1DM, treated with dapagliflozin, were included in the model validation: NCT02268214[42] and NCT02460978.[43] Patients received either a placebo or dapagliflozin 5 or 10 mg once daily as an add-on therapy to insulin for a 24-week short-term treatment period, followed by a 28-week long-term subject- and site-blinded treatment period. Throughout the study (from the beginning of the lead-in period to the end of the long-term treatment period), the insulin dose was adjusted consistent with good medical practice, according to self-measured blood glucose readings, local guidance, and individual circumstances. Patients were not allowed to change their insulin administration methods during the study period except during replacements of insulin pumps.

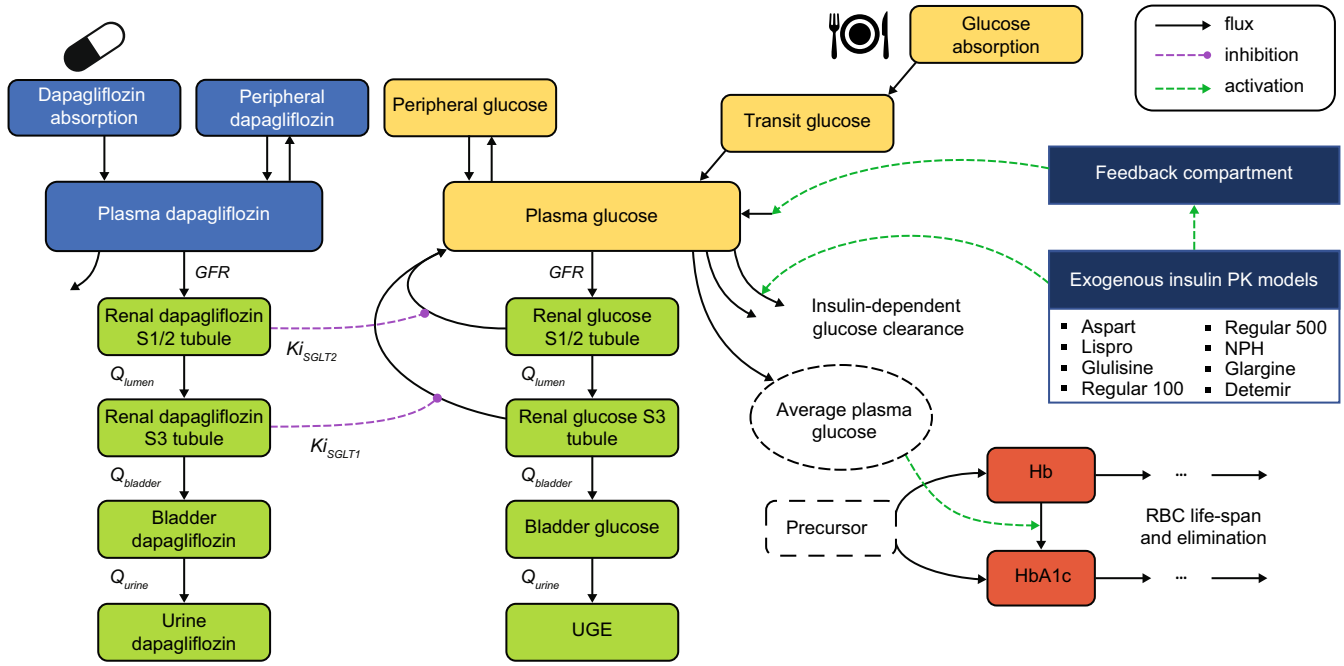

FIGURE 1 Schematic representation of the T1DM platform model, enhanced with PK models of exogenous insulins acting on the insulin-dependent glucose clearance. The dapagliflozin PK, integrated glucose-insulin, and renal models (blue, yellow, and green areas) were adapted, respectively, from Melin et al.,[14] Jauslin et al.,[17] and Yakovleva et al.[15]; the integrated glucose-RBC-HbA1c model (red area) was adapted from Lledó-García et al.[19] GFR, glomerular filtration rate; Hb, hemoglobin; HbA1c, glycated hemoglobin; Ki_{SGLT1}, affinity of an inhibitor to SGLT1; Ki_{SGLT2}, affinity of an inhibitor to SGLT2; NPH, neutral protamine Hagedorn; PK, pharmacokinetics; $Q_{bladder}$, flow rate to the bladder from the S3 segment; Q_{lumen}, flow rate between renal tubule segments; Q_{urine}, flow rate of urine from the bladder; RBC, red blood cell; SGLT1, type 1 sodium-glucose cotransporter; SGLT2, type 2 sodium-glucose cotransporter; T1DM, type 1 diabetes mellitus; UGE, urinary glucose excretion.

Pharmacodynamic data from the NCT02268214 and NCT02460978 dapagliflozin clinical trials were used to validate long-term responses in glycemic control (i.e., average plasma glucose at weeks 12 and 24 and HbA1c at weeks 4, 8, 12, 18, and 24), as predicted with the IGID-T1DM model considering the adjustment of the total daily insulin dose over the treatment period.

Model development

Adaptation of the T2DM modeling platform to describe the T1DM condition was performed sequentially. At the first step, differential equations reflecting endogenous insulin dynamics in plasma and effect compartment were removed and replaced by PK models for seven different types of insulin. Consequently, the endogenous insulin in the insulin-dependent glucose elimination rate was replaced with the sum of exogenous insulin concentrations.

At the second step, the parameters of the insulin-driven feedback on glucose production rate were estimated based on the aspart and lispro PK data with different protamine fractions (9 time series in total), and corresponding plasma glucose measurements made within 12 h after insulin dose administration. To achieve the best description of the plasma insulin concentration after lispro and aspart administration with different protamine fractions and to remove potential bias from the limitations of the generalized PK models, each PK curve was described by a unique set of parameters, mimicking the forcing function approach. Meal size and meal composition were adapted from the corresponding publications; however, to allow an additional degree of flexibility, a scalar parameter (representing the conversion of a meal in kcal to the model input) and the absorption rate from the gut were estimated. Because aspart and lispro administration was preceded with unknown doses of other insulins, 18-h regular 100 insulin infusion was simulated with an estimated dose to achieve the glucose level matching with the starting point of the glucose observations, as baseline glucose values cannot be represented as the initial conditions (i.e., steady-state) of the system that is constantly perturbed by meals and insulin doses. Finally, various structural models were evaluated, incorporating protamine fraction as a factor influencing either the magnitude of the insulin feedback or delay, or both.

Model selection was based on the following complex criterion: the difference in objective function value

(−2 log-likelihood) or Akaike information criterion between the nested or non-nested models should exceed −3.84 or 0, respectively; relative standard errors (RSEs) of the estimated parameters calculated from the Fisher information matrix should not exceed 50%; goodness-of-fit plots should provide an unbiased description of the data; multi-start parameter optimization procedure within the wide range of initial parameter values should result in the matching point estimates for most of the test runs.

Model development, analysis, validation, and forward simulations were performed using Monolix software (version 2020R1; Lixoft, France) and R software (version 4.0.2; R Project, www.r-project.org).

Model validation and forward simulations

First, PK profiles of aspart, lispro, regular insulin/NPH, and glargine were reproduced based on the integrated published PK models and compared with the observed data. Second, model validation was performed by predicting long-term glucose and HbA1c response for dapagliflozin phase III trials NCT02268214 and NCT02460978. Because individual information on daily food consumption, particular types of insulin administration, and times of insulin administration was not registered during the trials, a generalized scenario was proposed, with the 40 U total daily insulin dose being divided in a 60:40 ratio between the single morning dose of insulin glargine as basal insulin and 75%/25% soluble-to-protamine mixture of insulin aspart as bolus insulin given twice daily simultaneously with a meal equivalent of 165 g of glucose at 4 and 8 h after glargine administration. The changes in total insulin dose were measured at weeks 2, 12, and 24 and those measurements were incorporated into the simulations as a time-dependent stepwise function modifying the doses of all insulins. The observed changes in average daily plasma glucose and changes in HbA1c were compared with model-predicted values under treatment with placebo, dapagliflozin 5 mg, or dapagliflozin 10 mg daily.

Two types of sensitivity analyses were performed. In all cases, reference simulations were based on the scenarios of insulin and meal administration described above (i.e., 40 U of total daily insulin dose separated between basal and bolus insulins in a 60:40 ratio, and the meal equivalent of 165 g glucose given twice daily). Basic local sensitivity analysis was performed to analyze the effect of dapagliflozin treatment (10 mg daily) on 24-h glucose profiles under different meals and insulin administration times relative to the mealtime. Meal size varied within the 50% interval from the reference value of 165 g. Bolus insulin injection times ranged from 1 h before a meal to 1 h after a meal. In both sensitivity analyses, the insulin dose remained unchanged.

The other type of sensitivity analysis included calculation of the partial rank correlation coefficients (PRCCs) for a set of preselected model parameters against the dependent variables at baseline and at dapagliflozin treatment steady-state.[44] The values of 10 model parameters (including insulin dose adjustment, protamine fraction, meal size, steady-state glucose level, glucose absorption rate, insulin-dependent and insulin-independent glucose clearance, feedback parameters for insulin effects on glucose production increase, and life span of red blood cells) were sampled 500 times using Latin hypercube sampling from the predefined range (Table S2). Simulations were performed using the obtained values with subsequent calculation of the PRCC to identify the model inputs associated with the disease state (i.e., glycemic control at baseline) and dapagliflozin efficacy (i.e., precent change from baseline in daily mean glucose levels and HbA1c at the last day of week 24 of daily dapagliflozin 10 mg treatment).

Last, simulations with different scenarios of insulin dose adjustment were performed to evaluate the efficacy of dapagliflozin as an add-on therapy to insulin in detail. HbA1c and average plasma glucose concentration at week 52 of daily dapagliflozin 10 mg treatment were compared between the model prediction with the insulin dose adjusted in the range of −65% to +135% from the reference value of 40 U per day for subjects with different baseline HbA1c and glucose values.

RESULTS

The developed glulisine and detemir PK models described the data well, as judged from the goodness-of-fit plots (Figures S1 and S2). All parameters were estimated with reasonable precision (RSE < 50%), and the model converged to the same values in the multi-start parameter estimation procedure (Table S1). Published PK models of other types of insulins captured the trends in most of the observed data found in the literature (Figures S3–S6). However, for a few sources (e.g., Thorisdottir et al. 2009[23] for aspart or Owens et al. 2019[30] for glargine), overprediction or underprediction of the data can be observed.

Implementation of the insulin-driven feedback on glucose production allowed an adequately accurate description of the short-term glucose data (Figure 2a, Figure S7). Meal energy content scalar parameter and absorption from the gut, feedback parameters, and regular insulin dose, required to achieve the observed baseline glucose values, were reasonably well-estimated (Table S1). Protamine fraction was found to play a major role in glucose recovery

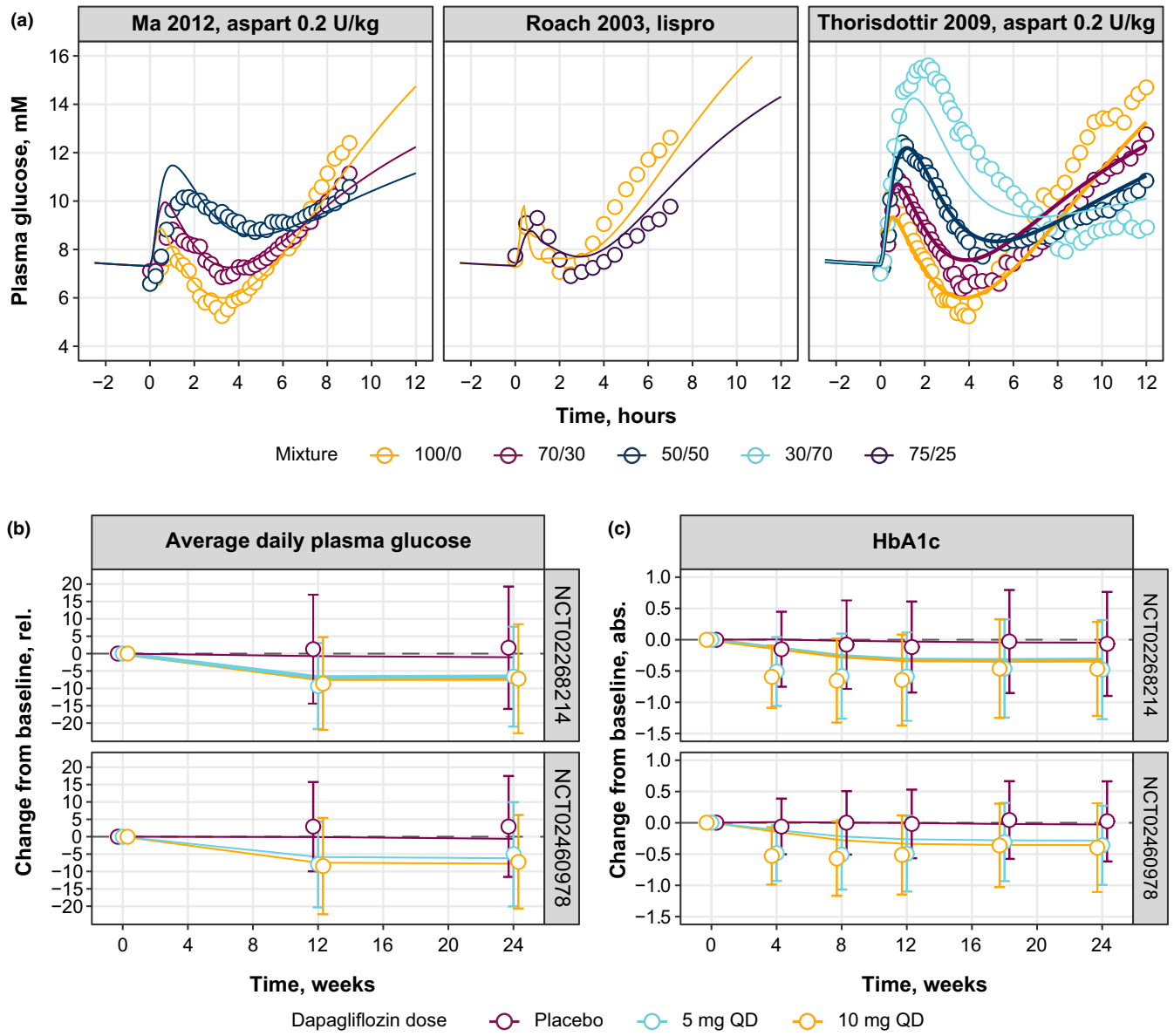

FIGURE 2 Validation of IGID model for the T1DM population. (a) Glucose short-term response to aspart and lispro insulins; (b) glucose; and (c) HbA1c long-term response to aspart and dapagliflozin treatment, mean ± SD. HbA1c, glycated hemoglobin; IGID, integrated glucose-insulin-dapagliflozin; mM, millimolar; QD, once daily; SD, standard deviation; T1DM, type 1 diabetes mellitus.

times and affected both magnitude and delay parameters of the insulin feedback, as well as insulin-mediated glucose clearance. Injection of the 50%/50% protamine mixture resulted in a 17.75% lower rate of the glucose clearance and feedback effect than injection of the soluble insulin; the onset of the feedback effect, however, was 18.15% faster for the mixture. The model-predicted long-term effects of combined dapagliflozin and insulin treatment reflected in the decline in average daily plasma glucose and HbA1c after 24 weeks of treatment were mostly consistent with the observed data from the NCT02268214 and NCT02460978 studies (Figure 2b).

Model simulations were used to explore the impact of different meal sizes and timing of insulin administration on daily glucose oscillations in two scenarios: control treatment (insulin only) and following 10 mg daily dapagliflozin (in addition to insulin; Figure 3). Changes in meal size primarily affected average levels of plasma glucose (up to ±1.1 mM or ± 13%) and maximum glucose levels (up to 4.5 mM or ± 35%), whereas minimum glucose levels remained unchanged. Dapagliflozin treatment resulted in the glucose concentration curve being downshifted by ~1 mM (11%) relative to the control, with maximum treatment benefit observed at maximum meal size (−1.2 mM), most likely as a consequence of the increased glucose availability in the kidneys (Figure 3a). In neither scenario (with or without dapagliflozin), glucose levels went below the threshold of hypoglycemia. Perturbations

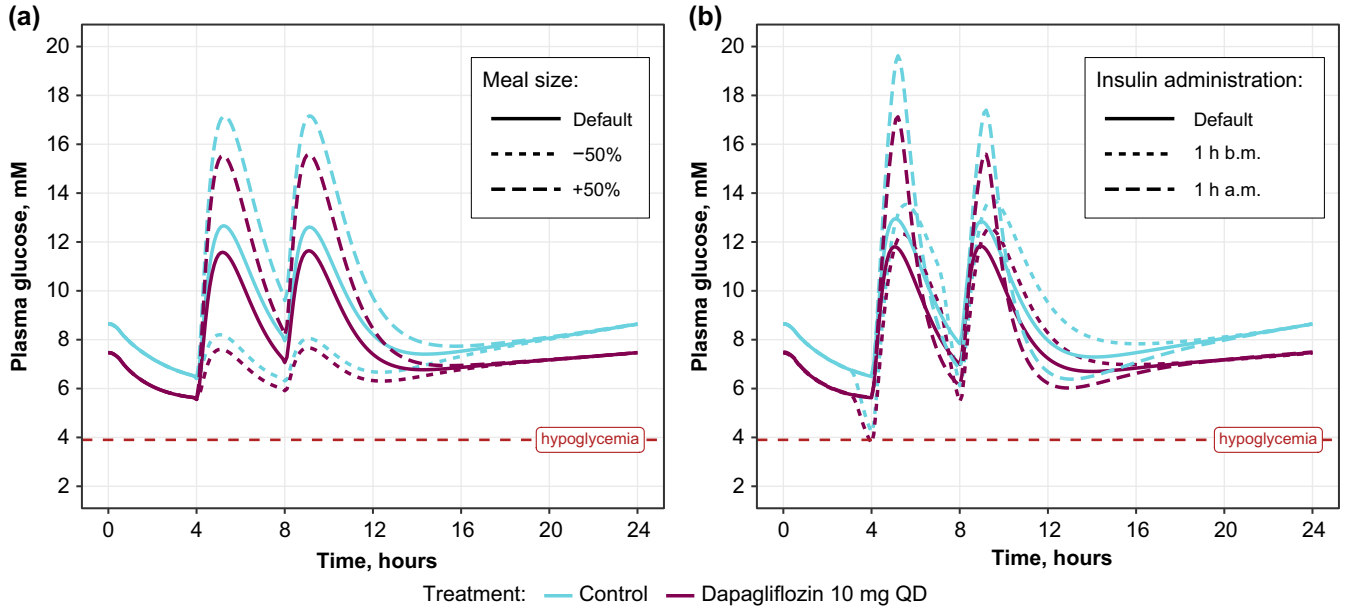

FIGURE 3 Intraday glucose oscillations under different meals (a) and insulin administration times (b) with and without dapagliflozin treatment. Default meal size, 165 g[42,43]; a.m., after a meal; b.m., before a meal; mM, millimolar; hypoglycemia threshold defined as 3.9 mM based on the Endocrine Society Clinical Practice Guideline.[52]

in the bolus insulin administration time relative to the meals did not alter the mean plasma glucose levels. However, marked changes were observed at 1 h before a meal in minimum (−2.327 mM or − 35%) and at 1 h after a meal in maximum glucose concentrations (+6.5 mM or + 50%). Consequently, the dapagliflozin effect varied between −0.45 and −2.5 mM depending on the glucose concentration at a particular time-period (Figure 3b). It can be noted that the combined effect of insulin and dapagliflozin in the latter case resulted in glucose lowering beyond the acceptable level of 3.9 mM, although only for ~5 min.

PRCC calculation for the model variables representing baseline and steady-state glucose and HbA1c levels under dapagliflozin treatment in response to the changes in selected model parameters showed that the behavior of the system is consistent with our general understanding of the glucose-insulin-HbA1c relationship and dapagliflozin efficacy (Figure 4). In particular, dapagliflozin treatment benefit was most sensitive to insulin dose adjustment. Furthermore, glucose clearance was positively associated with treatment efficacy (i.e., greater efficacy was observed in patients who had higher insulin-dependent glucose clearance). A reverse correlation was observed for the feedback of insulin on glucose production. The effect of disease severity (i.e., steady-state glucose) and meal size on percent change from baseline in mean glucose and HbA1c was not statistically significant, which is in line with the results of the local sensitivity analysis. However, both meal size and protamine fraction significantly affected the magnitude of glucose oscillations under treatment.

To explore the impact of insulin dose adjustment further, average plasma glucose levels and HbA1c responses to dapagliflozin 10 mg at week 52 were evaluated within a wide range of insulin dose adjustments, from −65% to +135%, for three baseline HbA1c levels (6%, 7.1%, and 8%; Figure 5). In a population with baseline HbA1c of 7.1%, dapagliflozin as an add-on therapy to insulin led to a 10.9% reduction in average plasma glucose levels from baseline and an average HbA1c reduction of 0.5% (absolute). Increasing the total daily insulin dose by 20% after dapagliflozin treatment initiation lowers the steady-state plasma glucose by an additional 6% and HbA1c by 0.787% (absolute) in total. Conversely, decreasing the total daily insulin dose by 20% after dapagliflozin treatment initiation resulted in a marginal 3% decrease in average plasma glucose and 0.126% (absolute) in HbA1c from baseline. These numbers are affected by the disease state parameters, with better response to the dapagliflozin treatment being observed in populations with worsened glycemic control. Depending on the baseline HbA1c level, a daily insulin dose reduction between 15% and 38% was found to be sufficient to counterbalance the average glucose reduction by dapagliflozin treatment in the T1DM population.

DISCUSSION

In this study, we adapted the existing systems pharmacology platform, originally developed to describe short- and long-term effects of dapagliflozin on glucose-related markers, to quantify the effects of combined insulin and dapagliflozin

treatment on glycemic control in T1DM. This extension considers the key differences in insulin-glucose homeostasis between the types of the disease through parsimonious tuning of the mathematical system and implementation of a broad spectrum of exogenous insulin PK models allowing to cover most insulin treatment cases.

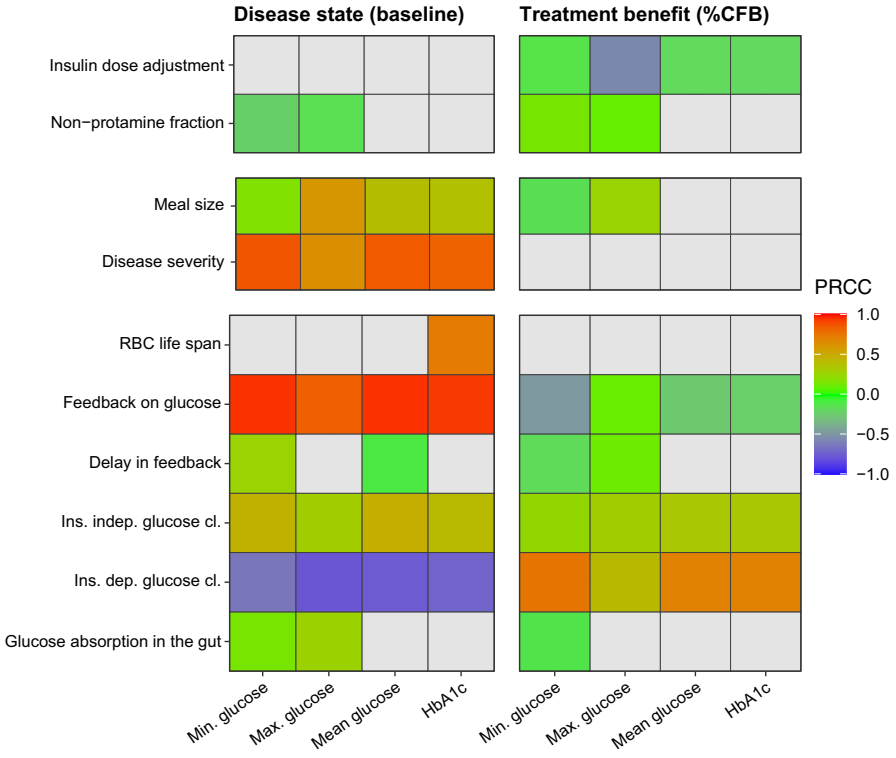

FIGURE 4 Sensitivity of model outputs to the selected model parameters based on partial rank correlation coefficients. Upper panels – therapeutic options; middle panels – patient management; bottom panels – intrinsic factors; %CFB, percent change from baseline; cl, clearance; dep, dependent; HbA1c, glycated hemoglobin; indep, independent; ins, insulin; RBC, red blood cell; Min. – minimum; Max. – maximum; gray color – p value > 0.05.

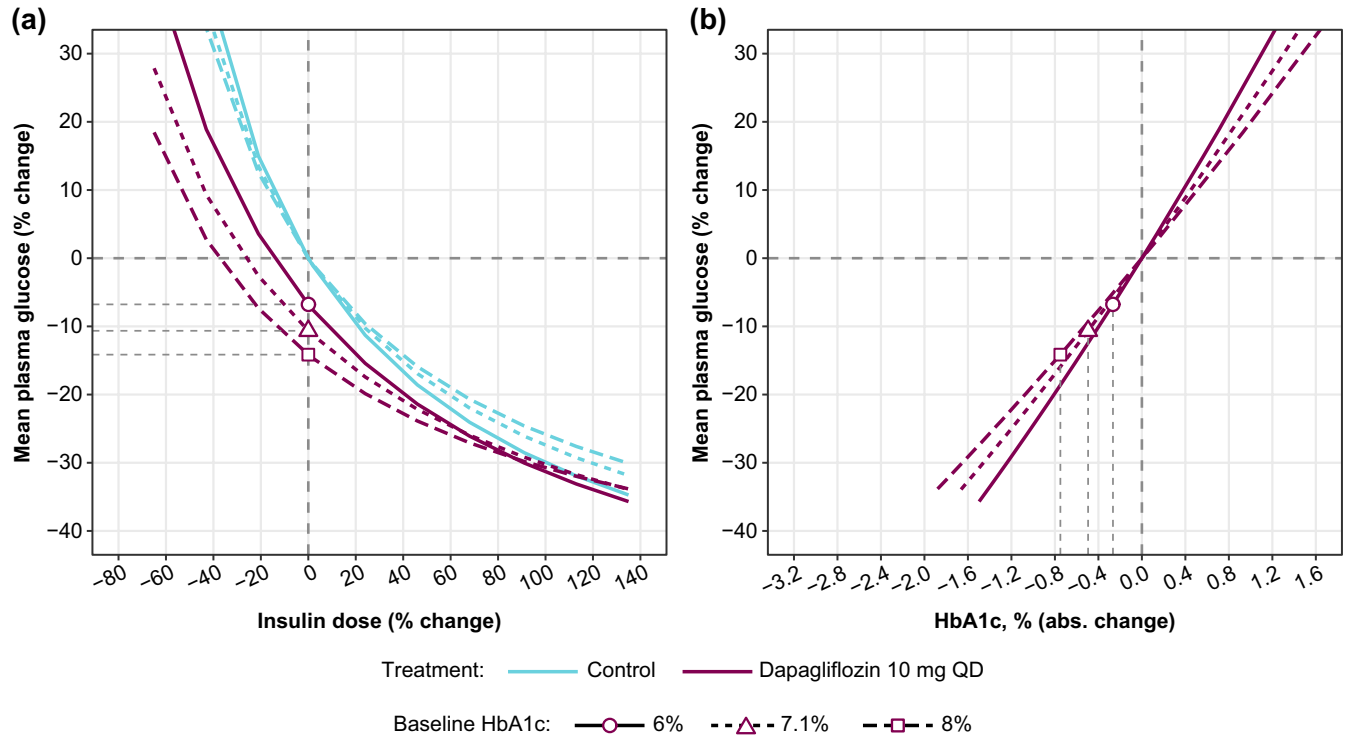

FIGURE 5 Impact of change in insulin dose on long-term benefits. (a) Impact of insulin dose on average plasma glucose and the relationship between average plasma glucose and (b) HbA1c. Points, dapagliflozin-mediated treatment benefit without insulin dose adjustment; curves, model predictions; thick gray dashed lines, zero axis lines (baseline); thin gray lines, projections from the points to the axes to illustrate dapagliflozin treatment effect; abs, absolute; HbA1c, glycated hemoglobin.

Insulin aspart, lispro, regular, NPH, and glargine PK were carefully reproduced using the published models and validated using literature data, or developed de novo, as in cases of insulin glulisine and detemir. The models were able to reproduce the overall trends in insulin PK data from various sources (Figures S3–S6), although the variability between the studies largely remains unexplained, as the sources of inter- and intrasubject variability in insulin PKs are manifold,[45] whereas the available publicly disclosed data are limited. The developed model captures the general behavior of the system; however, further refinement of the short-term predictions is necessary to derive posterior distributions based on random effects and make inference on the treatment efficacy and safety in the actual population.

Through subsequent model analysis, the necessity to alter glucose production rates to capture short-term glucose response to different rapid-acting insulins was revealed, addressed by introducing insulin-dependent feedback on glucose production. Furthermore, the rate of glucose recovery was markedly different between the protamine mixtures, which cannot be explained by the differences in insulin PKs alone (Figure 2a). One hypothetical explanation of this phenomenon is the lack of glucagon and associated effects in the model. Insulin acts as an inhibitor of glucagon secretion[46,47]; thus, the recovery of plasma glucose within 4–12 h after insulin administration might be related to the restoration of glucagon levels after initial inhibition and inversely depends on the peak insulin concentration.

As model simulations suggest, the prominent effect of insulin administration time on trough levels of plasma glucose combined with dapagliflozin-mediated glucose reduction might lower plasma glucose concentrations below the acceptable levels, suggesting that tighter control over insulin administration times is required for the combination treatment. By contrast, a two-fold decrease in meal energy content relative to the control under a stable insulin dose primarily affects the daily average and peak glucose levels. Thus, as long as the rate of insulin-dependent glucose clearance is compensated by the glucose appearance after a meal, hypoglycemia incidents should be avoided.

The model could describe the long-term benefits of dapagliflozin treatment when compared to the observed data from phase III clinical trials; however, the trend in the observed HbA1c data apparently follows a nonlinear pattern of an initial 0.6% decline (weeks 4–12) with a subsequent increase by ~0.2% (weeks 18–24), also noted in another publication.[48] Assuming that the insulin and dapagliflozin doses are stable throughout the 24-week period, the model is unable to capture this behavior. Unaccounted variability in the half-life of red blood cells might affect the onset of the steady-state but cannot explain the non-monotonous pattern in the data. Other possible hypotheses are related to the time-dependent changes in the insulin dose adjustment, dapagliflozin compliance, or glucose homeostasis. Available daily insulin dose and compliance data do not indicate such behavior. Because plasma glucose measurements in phase III studies were available only at weeks 12 and 24, the latter hypothesis is challenging to validate or refute; however, a similar HbA1c behavior in an empagliflozin-related modeling analysis was attributed to the time-dependent increase in mean daily glucose, although no mechanistic explanation was proposed.[49] Furthermore, no such trends were observed in T2DM.[50] Thus, any model-based inference regarding the time of onset of the dapagliflozin effect in the T1DM population should be treated cautiously.

Glucose homeostasis is a perplexing system associated with numerous feedbacks and regulatory mechanisms, different aspects of which were the subject of multiple model-based analyses.[13,51] The developed platform of this model enables the comparison of short-term and long-term treatment benefits for a range of dapagliflozin doses and several short- and long-acting exogenous insulins, also accounting for heterogeneity in insulin treatment scenarios, meals, and other factors in the actual population. Moreover, the model may serve as a quantitative tool for optimal dose selection and investigation of the underlying intricate physiological system. One of the potential opportunities for further model expansion is to assess the link between glucose/insulin homeostasis and the risk of diabetic ketoacidosis, a potentially life-threatening complication in patients with T1DM. Such extension could potentially give valuable insight into the risk of diabetic ketoacidosis during SGLT2 inhibitor treatment.

AUTHOR CONTRIBUTIONS

V.S., T.Y., L.S., and W.T. wrote the manuscript. V.S., R.C.P., D.B., J.P., and W.T. designed the research. V.S., T.Y., and L.S. performed the research. V.S., T.Y., L.S., R.C.P., J.P., and WT. analyzed the data.

ACKNOWLEDGMENTS

The authors would like to acknowledge the contribution of Maria Cristina Leon Atupana, PhD, an employee of M&S Decisions, to data collection and analysis. Riva Verma, PhD, of Cactus Life Sciences (part of Cactus Communications) provided editorial support, which was contracted and funded by AstraZeneca.

FUNDING INFORMATION

This study was funded by AstraZeneca.

CONFLICT OF INTEREST STATEMENT

V.S., T.Y., and L.S. are employees of M&S Decisions LLC, a modeling consultancy contracted by AstraZeneca. T.Y. owns AstraZeneca stock or stock options. R.C.P., D.B., J.P., and W.T. are employees of AstraZeneca and own AstraZeneca stock or stock options.

ORCID

Victor Sokolov https://orcid.org/0000-0001-7066-0811
Tatiana Yakovleva https://orcid.org/0000-0002-9715-0931
Leonid Stolbov https://orcid.org/0000-0002-3258-8350
Robert C. Penland https://orcid.org/0000-0003-2706-8913

REFERENCES

1. Sarwar N, Gao P, Seshasai SRK, et al. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. *Lancet*. 2010;375:2215-2222.
2. American Diabetes Association. Statistics about diabetes. 2017. Available at: https://diabetes.org/about-us/statistics/about-diabetes. Accessed 19 January 2023.
3. Galicia-Garcia U, Benito-Vicente A, Jebari S, et al. Pathophysiology of type 2 diabetes mellitus. *Int J Mol Sci*. 2020;21:6275.
4. American Diabetes Association. 2. Classification and diagnosis of diabetes: standards of medical care in diabetes-2020. *Diabetes Care*. 2020;43:S14-S31.
5. Wysham C, Shubrook J. Beta-cell failure in type 2 diabetes: mechanisms, markers, and clinical implications. *Postgrad Med*. 2020;132:676-686.
6. Miller KM, Foster NC, Beck RW, et al. Current state of type 1 diabetes treatment in the U.S.: updated data from the T1D exchange clinic registry. *Diabetes Care*. 2015;38:971-978.
7. Lind M, Svensson AM, Kosiborod M, et al. Glycemic control and excess mortality in type 1 diabetes. *N Engl J Med*. 2014;371:1972-1982.
8. Niswender KD. Basal insulin: physiology, pharmacology, and clinical implications. *Postgrad Med*. 2011;123:17-26.
9. Abdul-Ghani MA, Matsuda M, Balas B, DeFronzo RA. Muscle and liver insulin resistance indexes derived from the oral glucose tolerance test. *Diabetes Care*. 2007;30:89-94.
10. Komoroski B, Vachharajani N, Boulton D, et al. Dapagliflozin, a novel SGLT2 inhibitor, induces dose-dependent glucosuria in healthy subjects. *Clin Pharmacol Ther*. 2009;85:520-526.
11. Komoroski B, Vachharajani N, Feng Y, Li L, Kornhauser D, Pfister M. Dapagliflozin, a novel, selective SGLT2 inhibitor, improved glycemic control over 2 weeks in patients with type 2 diabetes mellitus. *Clin Pharmacol Ther*. 2009;85:513-519.
12. List JF, Woo V, Morales E, Tang W, Fiedorek FT. Sodium-glucose cotransport inhibition with dapagliflozin in type 2 diabetes. *Diabetes Care*. 2009;32:650-657.
13. Ajmera I, Swat M, Laibe C, Le Novère N, Chelliah V. The impact of mathematical modeling on the understanding of diabetes and related complications. *CPT Pharmacometrics Syst Pharmacol*. 2013;2:e54.
14. Melin J, Tang W, Rekić D, et al. Dapagliflozin pharmacokinetics is similar in adults with type 1 and type 2 diabetes mellitus. *J Clin Pharmacol*. 2022;62:1227-1235.
15. Yakovleva T, Sokolov V, Chu L, et al. Comparison of the urinary glucose excretion contributions of SGLT2 and SGLT1: a quantitative systems pharmacology analysis in healthy individuals and patients with type 2 diabetes treated with SGLT2 inhibitors. *Diabetes Obes Metab*. 2019;21:2684-2693.
16. Silber HE, Jauslin PM, Frey N, Gieschke R, Simonsson USH, Karlsson MO. An integrated model for glucose and insulin regulation in healthy volunteers and type 2 diabetic patients following intravenous glucose provocations. *J Clin Pharmacol*. 2007;47:1159-1171.
17. Jauslin PM, Silber HE, Frey N, et al. An integrated glucose-insulin model to describe oral glucose tolerance test data in type 2 diabetics. *J Clin Pharmacol*. 2007;47:1244-1255.
18. Silber HE, Frey N, Karlsson MO. An integrated glucose-insulin model to describe oral glucose tolerance test data in healthy volunteers. *J Clin Pharmacol*. 2010;50:246-256.
19. Lledó-García R, Mazer NA, Karlsson MO. A semi-mechanistic model of the relationship between average glucose and HbA1c in healthy and diabetic subjects. *J Pharmacokinet Pharmacodyn*. 2013;40:129-142.
20. Shah M, Stolbov L, Yakovleva T, et al. A model-based approach to investigating the relationship between glucose-insulin dynamics and dapagliflozin treatment effect in patients with type 2 diabetes. *Diabetes Obes Metab*. 2021;23:991-1000.
21. Steele C, Hagopian WA, Gitelman S, et al. Insulin secretion in type 1 diabetes. *Diabetes*. 2004;53:426-433.
22. Røge RM, Klim S, Kristensen NR, Ingwersen SH, Kjellsson MC. Modeling of 24-hour glucose and insulin profiles in patients with type 2 diabetes mellitus treated with biphasic insulin aspart. *J Clin Pharmacol*. 2014;54:809-817.
23. Tham LS, Schneck K, Ertekin A, Reviriego J. Modeling pharmacokinetic profiles of insulin regimens to enhance understanding of subcutaneous insulin regimens. *J Clin Pharmacol*. 2017;57:1126-1137.
24. Monnier L, Colette C, Dunseath GJ, Owens DR. The loss of postprandial glycemic control precedes stepwise deterioration of fasting with worsening diabetes. *Diabetes Care*. 2007;30:263-269.
25. Lindholm A, McEwen J, Riis AP. Improved postprandial glycemic control with insulin aspart. A randomized double-blind cross-over trial in type 1 diabetes. *Diabetes Care*. 1999;22:801-805.
26. Lindström T, Hedman CA, Arnqvist HJ. Use of a novel double-antibody technique to describe the pharmacokinetics of rapid-acting insulin analogs. *Diabetes Care*. 2002;25:1049-1054.
27. Ma Z, Parkner T, Frystyk J, Laursen T, Lauritzen T, Christiansen JS. A comparison of pharmacokinetics and pharmacodynamics of insulin aspart, biphasic insulin aspart 70, biphasic insulin aspart 50, and human insulin: a randomized, quadruple crossover study. *Diabetes Technol Ther*. 2012;14:589-595.
28. Thorisdottir RL, Parkner T, Chen JW, Ejskjaer N, Christiansen JS. A comparison of pharmacokinetics and pharmacodynamics of biphasic insulin aspart 30, 50, 70 and pure insulin aspart: a randomized, quadruple crossover study. *Basic Clin Pharmacol Toxicol*. 2009;104:216-221.
29. Petersen SB, Kildegaard J, Nielsen FS, et al. Pharmacokinetics following continuous subcutaneous insulin infusion of insulin aspart with or without initial subcutaneous bolus. *Diabetes Obes Metab*. 2010;12:334-340.

30. Ihlo CA, Lauritzen T, Sturis J, Skyggebjerg O, Christiansen JS, Laursen T. Pharmacokinetics and pharmacodynamics of different modes of insulin pump delivery. A randomized, controlled study comparing subcutaneous and intravenous administration of insulin aspart. *Diabet Med.* 2011;28:230-236.
31. de la Peña A, Yeo KP, Linnebjerg H, et al. Subcutaneous injection depth does not affect the pharmacokinetics or glucodynamics of insulin lispro in normal weight or healthy obese subjects. *J Diabetes Sci Technol.* 2015;9:824-830.
32. Jacobs MA, Keulen ET, Kanc K, et al. Metabolic efficacy of preprandial administration of Lys(B28), pro(B29) human insulin analog in IDDM patients. A comparison with human regular insulin during a three-meal test period. *Diabetes Care.* 1997;20:1279-1286.
33. Kapitza C, Nowotny I, Lehmann A, et al. Similar pharmacokinetics and pharmacodynamics of rapid-acting insulin lispro products SAR342434 and US- and EU-approved Humalog in subjects with type 1 diabetes. *Diabetes Obes Metab.* 2017;19:622-627.
34. Leohr J, Dellva MA, LaBell E, et al. Pharmacokinetic and glucodynamic responses of ultra rapid lispro vs lispro across a clinically relevant range of subcutaneous doses in healthy subjects. *Clin Ther.* 2020;42:1762-1777.
35. Roach P, Woodworth J, Gudat U, et al. A 75% insulin lispro/25% NPL mixture provides a longer duration of insulin activity compared with insulin lispro alone in patients with type 1 diabetes. *Diabet Med.* 2003;20:946-952.
36. Shiramoto M, Nasu R, Oura T, Imori M, Ohwaki K. Ultra-rapid Lispro results in accelerated insulin lispro absorption and faster early insulin action in comparison with Humalog(®) in Japanese patients with type 1 diabetes. *J Diabetes Investig.* 2020;11:672-680.
37. Heinemann L, Linkeschova R, Rave K, Hompesch B, Sedlak M, Heise T. Time-action profile of the long-acting insulin analog insulin glargine (HOE901) in comparison with those of NPH insulin and placebo. *Diabetes Care.* 2000;23:644-649.
38. Owens DR, Bailey TS, Fanelli CG, Yale JF, Bolli GB. Clinical relevance of pharmacokinetic and pharmacodynamic profiles of insulin degludec (100, 200 U/mL) and insulin glargine (100, 300 U/mL) - a review of evidence and clinical interpretation. *Diabetes Metab.* 2019;45:330-340.
39. Becker RHA. Insulin glulisine complementing basal insulins: a review of structure and activity. *Diabetes Technol Ther.* 2007;9:109-121.
40. Danne T, Lüpke K, Walte K, Von Schuetz W, Gall MA. Insulin detemir is characterized by a consistent pharmacokinetic profile across age-groups in children, adolescents, and adults with type 1 diabetes. *Diabetes Care.* 2003;26:3087-3092.
41. Jhee SS, Lyness WH, Rojas PB, Leibowitz MT, Zarotsky V, Jacobsen LV. Similarity of insulin detemir pharmacokinetics, safety, and tolerability profiles in healthy Caucasian and Japanese American subjects. *J Clin Pharmacol.* 2004;44:258-264.
42. AstraZeneca. A multicenter, randomized, double-blind, placebo-controlled, parallel group, phase 3 study to evaluate the efficacy and safety of dapagliflozin as an add-on to insulin therapy in subjects with type 1 diabetes mellitus. 2018. https://clinicaltrials.gov/ct2/show/NCT02268214. Accessed 19 January 2023.
43. AstraZeneca. A multicenter, randomized, double-blind, placebo-controlled, parallel group, phase 3 study to evaluate the efficacy and safety of dapagliflozin as an add-on to insulin therapy in subjects with type 1 diabetes mellitus - study two. 2019. Available at: https://clinicaltrials.gov/ct2/show/NCT02460978. Accessed 19 January 2023.
44. Marino S, Hogue IB, Ray CJ, Kirschner DE. A methodology for performing global uncertainty and sensitivity analysis in systems biology. *J Theor Biol.* 2008;254:178-196.
45. Heinemann L. Variability of insulin absorption and insulin action. *Diabetes Technol Ther.* 2002;4:673-682.
46. Bansal P, Wang Q. Insulin as a physiological modulator of glucagon secretion. *Am J Physiol Endocrinol Metab.* 2008;295:E751-E761.
47. Vergari E, Knudsen JG, Ramracheya R, et al. Insulin inhibits glucagon release by SGLT2-induced stimulation of somatostatin secretion. *Nat Commun.* 2019;10:139.
48. Parkinson J, Tang W, Åstrand M, et al. Model-based characterization of the relationship between dapagliflozin systemic exposure and HbA1c response in patients with type 1 diabetes mellitus. *Diabetes Obes Metab.* 2019;21:1381-1387.
49. Johnston CK, Eudy-Byrne RJ, Elmokadem A, et al. A model-informed drug development (MIDD) approach for a low dose of empagliflozin in patients with type 1 diabetes. *Pharmaceutics.* 2021;13:485.
50. Bailey CJ, Gross JL, Pieters A, Bastien A, List JF. Effect of dapagliflozin in patients with type 2 diabetes who have inadequate glycaemic control with metformin: a randomised, double-blind, placebo-controlled trial. *Lancet.* 2010;375:2223-2233.
51. Mari A, Tura A, Grespan E, Bizzotto R. Mathematical modeling for the physiological and clinical investigation of glucose homeostasis and diabetes. *Front Physiol.* 2020;11:575789.
52. Cryer PE, Axelrod L, Grossman AB, et al. Evaluation and management of adult hypoglycemic disorders: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab.* 2009;94:709-728.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Sokolov V, Yakovleva T, Stolbov L, et al. A mechanistic modeling platform of SGLT2 inhibition: Implications for type 1 diabetes. *CPT Pharmacometrics Syst Pharmacol.* 2023;12:831-841. doi:10.1002/psp4.12956